

PATENT SPECIFICATION

(11) 1 390 479

1 390 479

(21) Application No. 41836/73 (22) Filed 5 Sept. 1973
 (44) Complete Specification published 16 April 1975
 (51) INT CL² A61K 31/35
 (52) Index at acceptance
 A5B 383 38Y 392 39X 501 502 50Y 540 54Y 566 56Y 606
 60Y 653 65Y 77Y
 (72) Inventors SOLOMON ARONOVICH GILLER, YANIS
 JURIEVICH POLL and ISAIAK MOISEEVICH
 KAMYANOV



(54) PHARMACEUTICAL COMPOSITION FOR TREATMENT
 OF PARKINSONISM

(71) We, ORDENA TRUDOVOGO KRASNOGO ZNAMENI INSTITUT ORGANICHESKOGO SINTEZA AKADEMII NAUK LATVIISKOI SSR, a body corporate organised under the laws of the USSR, of ulitsa Aizkraukles 21, Riga, USSR, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a pharmaceutical composition possessing anti-parkinson activity.

Known pharmaceuticals for treatment of parkinsonism include L-dopa, amantadine, and cholinolytic preparations. These known pharmaceuticals whether administered alone or in the form of a mixture have serious disadvantages.

For example, L-dopa has to be administered in large doses and produces undesirable side effects which become more serious as the daily dosage increases. Dyspeptic phenomena, such as nausea, vomiting, and pains in the stomach region, are the most common side effects. Cardiovascular dysfunction and eye disorders may also be observed. Many patients manifest psychic disorders and changes of the hemopoietic system. Side effects associated with L-dopa therapy have been found to occur in 90 percent of patients treated.

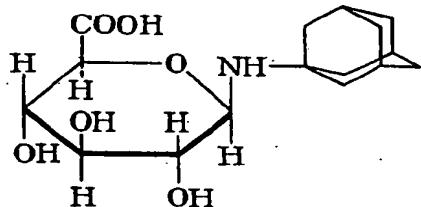
Amantadine has proved to be ineffective in some cases and exerts only an insignificant effect on certain symptoms of the disease: for example, it has little effect as regards lessening tremor.

Various cholinolytic preparations, for example, artane, have been used for treating parkinsonism. However, like the other cholinolytic preparations, artane produces undesirable effects: accommodation disorders, dryness in the mouth, constipation, and tachycardia. Cases have been reported in which narcomania developed following the administration of artane.

We have now developed a pharmaceutical composition which has high anti-parkinson

activity, and produces no, or substantially no, side effects.

According to the invention, there is provided a pharmaceutical composition having anti-parkinson activity, which comprises, as active principle, 1-adamantylamino-N-glucuronide of the formula:



together with an inert, solid, pharmaceutically acceptable carrier.

The active principle is a white crystalline material, soluble in water to the extent of 25 g/litre at 20° C. The melting point of the compound is 175° to 180° C, with decomposition.

Compositions of the invention are preferably made up in the form of tablets, dragees, capsules, troches, or suppositories.

A preferred pharmaceutical carrier for use in compositions of the invention particularly when the composition is in tablet form, is a mixture of stearic acid, lactose, potato starch and talc.

Preferably, the content of the active principle is from 10 to 600 mg, and more preferably about 200 mg, per unit dosage form.

It is possible to use the composition of the invention together with cholinolytic preparations, tricyclic anti-depressants, and also with benzodiazepine derivatives, in which case the therapeutic activity of the pharmaceutical composition according to the invention is increased.

We have found that when 1-adamantylamino-N-glucuronide is administered intraperitoneally to albino mice in doses of 800

[Price 33p]

mg/kg body weight, no appreciable changes in the behaviour of the mice are observed. The Table below shows the results of a comparative study of the effect of the active

principle of compositions of the invention, and of amantadine on the body temperature and the co-ordination of movements in albino mice ($P=0.05$).

5

Table

| Compound | Dose of compound at which a hypothermic effect is observed. | ED ₅₀ mg/kg body weight. Disordered co-ordination established. | |
|---------------------------------|---|---|----------------|
| | | By 'rotary rod' method | By 'tube' test |
| Amantadine | 75(61-93) | 64 (49-83) | 70 (51-97) |
| 1-adamantyl-amino-N-glucuronide | 1200 | 1000 | 1050(700-1587) |

10 The tabulated data show that while amantadine produces a hypothermic effect at a dose rate of 75 (61—93) mg/kg, the active principle of compositions of the invention produces a hypothermic effect only when administered in a dose of 1200 mg/kg body weight.

15 The active principle of compositions of the invention has an effect on the co-ordination of movements of albino mice only when administered in doses about 15 times greater than the dose of amantadine which affects the co-ordination of movements of the mice.

20 The LD₅₀ of amantadine for albino mice is 1150 mg/kg (peroral administration), while LD₅₀ for the active principle of compositions of the invention is 15,000 mg/kg body weight. When administered intraperitoneally, the LD₅₀ of amantadine for albino mice is 230 mg/kg, whilst all the mice to which 1-adamantyl-amino-N-glucuronide was given survived. In other words, 1-adamantylamino-N-glucuronide may be administered in doses five times greater than the LD₅₀ of amantadine, without producing any toxic effect in albino mice.

25 Unlike amantadine, 1-adamantylamino-N-glucuronide when administered in doses 20 to 30 mg/kg body weight does not affect the blood pressure or respiration, nor does it produce any effect on the M-, and N-cholino-, histamino-, or adrenoreactive systems.

30 The results of the experiments *in vivo* were confirmed by clinical investigations, which are illustrated by the following Examples.

Example 1.
A female patient of 56 was admitted to a hospital with schizophrenia. In the course of psycho-pharmacological therapy, a marked neuroleptic parkinsonism developed. The patient was given 3 doses a day of a composition of the invention for ten successive days, each dose containing 200 mg of 1-adamantylamino-N-glucuronide. The symptoms of parkinsonism gradually subsided and completely disappeared by the tenth day. No side effects were observed.

45

Example 2.
A female patient of 46 was admitted with postencephalitic parkinsonism, characterised by muscular rigidity and tremor (manifested form). The patient could not control herself. A composition of the invention was administered to the patient for a month, three doses being administered per day and each dose containing 200 mg of 1-adamantylamino-N-glucuronide. The basic symptoms of parkinsonism subsided in the course of the therapy and disappeared completely by the end of the month. Only insignificant hand tremor persisted. The patient continued to take the composition and no side effects were observed.

50

60

65

70

Example 3.
A male patient of 62 was admitted to hospital with atherosclerotic parkinsonism

(rigidity-tremor syndrome) in the manifested form. The patient had been bedridden for the greater part of each day. A composition of the invention was administered to the patient, the daily dose of 1-adamantylamino-N-glucuronide being 200 mg. The parkinsonism symptoms were markedly reduced after a few days. After 30 days, the therapy also included the use of artane, amitriptyline and seduxen (diazepam). The condition of the patient improved markedly. No side effects were noted.

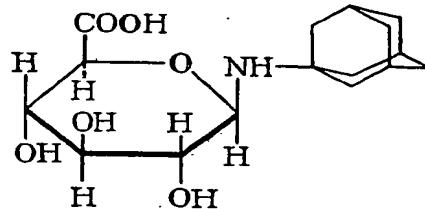
We have found that compositions of the invention have been efficacious in treating all the cases of parkinsonism so far investigated. However, the greatest efficacy of the compositions has been observed in the case of atherosclerotic and neuroleptic syndromes. Less efficacy was observed with Parkinson's disease and postencephalitic parkinsonism.

Compositions of the invention do not produce side effects when administered in doses up to 600 mg of the active principle, so that they are superior in this respect to L-dopa. Compositions of the invention are well tolerated by patients and improve their psychic condition. There are no contra-indications to the use of the compositions of the invention. The compositions, for example in the form of tablets or powders, may be stored indefinitely under normal conditions.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition having

anti-parkinson activity, which comprises, as active principle, 1-adamantylamino-N-glucuronide of the formula:



together with an inert, solid, pharmaceutically acceptable carrier.

2. A pharmaceutical composition according to claim 1, which is in the form of tablets, dragees, capsules, troches, or suppositories.

3. A pharmaceutical composition according to claim 1 or 2, in which the carrier is a mixture of stearic acid, lactose, potato starch and talc.

4. A pharmaceutical composition according to any of claims 1 to 3, which comprises from 10 to 600 mg of the active principle per unit dosage form.

A. A. THORNTON & CO.,

Chartered Patent Agents,

Northumberland House,

303/306 High Holborn, London, W.C.1.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1975.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.